REMARKS

Claims 25 and 33-35 are pending in the subject application. Applicants have canceled claims 33-35 without prejudice or disclaimer. Support for the amendment to claim 25 can be found in the specification at, *inter alia*, page 17, lines 19-25, page 23, line 15 to page 24, line 38, and page 113, lines 28-38. Applicants maintain that this the amendment to claim 25 raises no issue of new matter. Therefore, upon entry of this Amendment, claim 25 will be pending and under examination.

Objection to the Specification

The Examiner objected to the priority paragraph of the subject application as amended in the October 22, 2003 Preliminary Amendment. Specifically, the Examiner states that claims to priority of non-provisional applications must indicate the relationship between the applications.

In response, and without conceding the correctness of the Examiner's objection, applicants have amended the benefit claim in the first paragraph of the application to state that PCT International Application No. PCT/US99/07175 is a continuation-in-part of U.S. Serial No. 09/053,871. Accordingly, applicants maintain that the Examiner's objection has been obviated.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 25 and 33-35 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement

requirement. Specifically, the Examiner alleges that there is not sufficient direction or guidance provided by the specification to assist one skilled in the art in the selection of any "Factor IXa compound" that is effective for treating all reperfusion injuries, nor is there sufficient evidence provided that all such compounds are effective for treating all reperfusion injuries, in view of the broad definition of Factor IXa compound disclosed in the specification.

In response to the rejection of claims 33-35, applicants note that these claims have been canceled. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claim 25, and without conceding the correctness of the Examiner's rejection, applicants note that claim 25, as amended, provides a method for treating a reperfusion injury in a subject which comprises administering to the subject a Factor IXa compound in a sufficient amount over a sufficient period of time to inhibit coagulation so as to treat the reperfusion injury in the subject, wherein the Factor IXa compound is selected from the group consisting of the following: Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone, Factor IXmi (Ser365→Xxx), Factor IXmi (Asp269→Yyy), Factor IXmi (His221→Zzz), Factor IXmi (Ser365→Xxx, Asp269→Yyy), Factor IXmi (Ser365→Xxx, His221→Zzz), Factor IXmi (Asp269→Yyy, His221→Zzz), Factor IXmi (Ser365→Xxx, Asp269→Yyy, His221→Zzz), Factor IXami (Ser365→Xxx), Factor IXami (Asp269→Yyy), Factor IXami (His221→Zzz), Factor IXami (Ser365→Xxx, Asp269→Yyy), Factor IXami (Ser365→Xxx, His221→Zzz), Factor IXami (Asp269→Yyy, His221→Zzz) and Factor IXami (Ser365→Xxx, Asp269→Yyy, His221→Zzz), wherein Xxx is any one of the standard

amino acids other than serine, Yyy is any one of the standard amino acids other than aspartic acid and Zzz is any one of the standard amino acids other than histidine. Accordingly, amended claim 25 does not encompass the entire genus of Factor IXa compounds. Applicants maintain that the specification enables one skilled in the art to make and use the specific Factor IXa compounds recited in claim 25 for the claimed method.

The Examiner further alleged that even minor structural differences due to amino acid substitutions at one or more of amino acids Ser365, Asp269 and His221 of Factor IXa can result in substantially different biological and pharmacological activities affecting clot formation and hemostatis. In support of his position, the Examiner cites Brandstetter et al. which he claims was submitted with applicants' January 3, 2005 Information Disclosure Statement (IDS). Applicants note that no reference by Brandstetter et al. was submitted in their January 3, 2005 IDS and understand the Examiner to be referring to the Brandstetter et al. reference submitted with applicant's June 15, 2004 IDS.

In response, applicants note that although Brandstetter et al. briefly discuss Ser365 and His221, they do not discuss Asp269. Applicants note that the discussion of Ser365 and His221 in Brandstetter et al. is limited only to fact that the PPACK inhibitor is covalently linked thereto. Brandstetter et al. do not teach that amino acid substitutions of Ser365 and His221 result in substantially different biological and pharmacological activities affecting clot formation and hemostatis, as alleged by the Examiner.

Applicants further note that amended claim 25 recites, in part, a Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone, which the Examiner acknowledges on page 5 of the November 17, 2006 Office Action to be a working example of a Factor IXa compound.

The Examiner further rejects claims 25 and 33-35 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that claim 25 recites a method that utilizes a genus of molecules, i.e., Factor IXa compounds, but that the specification does not teach a core structure that is common to all Factor IXa compounds, or what structure or structures give rise to the disclosed function of Factor IXa compounds.

In response to the rejection of claims 33-35, applicants note that these claims have been canceled. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claim 25, applicants again note that claim 25, as amended, does not encompass the entire genus of Factor IXa compounds, but rather a Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone and specific muteins of Factor IXa. Applicants maintain that a Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone is sufficiently described in the specification (e.g. page 113, lines 28-38), as are the specific muteins of Factor IXa recited in amended claim 25 (e.g. page 23, line 15 to page 24, line 38). Accordingly, applicants maintain that one skilled in the art would reasonably conclude that the inventors, at the time the application

was filed, had possession of the claimed invention.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 25 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 25 and 33-35 under 35 U.S.C. 103(a) as allegedly obvious over Toledo-Pereya, in view of Benedict, et al. and King.

Specifically, the Examiner alleges that Toledo-Pereya teaches that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in reperfusion injury that needs to be treated with pharmacological agents to inhibit coagulation. However, the Examiner concedes on page 8 of the Office Action that Toledo-Pereya fails to teach the administration of Factor IXa compounds to treat thrombosis in reperfusion injury.

To cure this deficiency of Toledo-Pereya, the Examiner cites Benedict, et al. and King. The Examiner alleges that Benedict, et al. teach that inactivated Factor IXa was successful for inhibiting thrombus formation *in vivo*. The Examiner further alleges that King teaches the manufacture of inactivated blood factors, e.g., Factor IXa, using recombinant means. Accordingly, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to administer inactivated recombinant Factor IXa to patients to treat reperfusion injury.

In response to the rejection of claims 33-35, applicants note that these claims have been canceled. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claim 25, applicants note that nowhere do Toledo-Pereya, Benedict, et al. or King teach or suggest a Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone or the specific muteins recited in the claimed method. As discussed above, the Examiner concedes that Toledo-Pereya fails to teach the administration of Factor IXa compounds to treat thrombosis in reperfusion injury. Applicants note that the inactivation of Factor IXa described in Benedict, et al. was not due to amino acid substitutions at residues Ser365, Asp269 or His221 as recited in the claimed method, but rather via incubation of Factor IXa with glutamyl-glycyl-arginyl-chloromethylketone (see first paragraph under "Materials" on page 1760, column 2). Applicants also note that Benedict, et al. does not teach or suggest dansyl-glu-gly-arg-chloromethylketone chemical inactivation of Factor IXa. Accordingly, nowhere does Benedict, et al. teach or suggest the Factor IXa compounds recited in claim 25. Similarly, nowhere does King teach or suggest a Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone or the amino acid substitutions of the specific muteins recited in claim 25. Accordingly, applicants maintain that claim 25 is not obvious over Toledo-Pereya, in view of Benedict, et al. and King.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 25 under 35 U.S.C. §103(a).

Double Patenting Rejection

The Examiner further rejected claims 22 and 33-35 on the ground of nonstatutory obviousness-type double patenting over claims 1-19 of U.S. Patent No. 6,316,403 ("the '403 patent") in view of Toledo-Pereya and King. The '403 patent recites methods of treating ischemic disorders by administering inactivated Factor IXa to a patient to inhibit coagulation. The Examiner alleges that although the claims of the '403 patent fails to specifically recite reperfusion injury or recombinant inactivated Factor IXa, the claimed method recited in claim 25 is nonetheless obvious in light of the teachings of Toledo-Pereya and King discussed above.

In response to the rejection of claims 33-35, applicants note that these claims have been canceled. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claim 25, applicants again note that amended claim 25 provides, in part, a method for treating reperfusion injury in a subject which comprises administering to the subject a Factor IXa compound, wherein the Factor IXa compound is selected from the group consisting of the following: Factor IXa chemically inactivated by dansyl-glu-gly-arg-chloromethylketone, Factor IXmi (Ser365→Xxx), Factor IXmi (Asp269→Yyy), Factor IXmi (His221→Zzz), Factor IXmi (Ser365→Xxx, Asp269→Yyy), Factor IXmi (Ser365→Xxx, His221→Zzz), Factor IXmi (Asp269→Yyy, His221→Zzz), Factor IXmi (Ser365→Xxx, Asp269→Yyy, His221→Zzz), Factor IXami (Ser365→Xxx), Factor IXami (Asp269→Yyy), Factor IXami (His221→Zzz), Factor IXami (Ser365→Xxx, Asp269→Yyy), Factor IXami (Ser365→Xxx, His221→Zzz), Factor IXami (Asp269→Yyy, His221→Zzz) and Factor IXami

(Ser365→Xxx, Asp269→Yyy, His221→Zzz), wherein Xxx is any one of the standard amino acids other than serine, Yyy is any one of the standard amino acids other than aspartic acid and Zzz is any one of the standard amino acids other than histidine. Accordingly, applicants maintain that the claims of the '403 patent do not anticipate or render obvious the Factor IXa compounds recited in the claimed method. Furthermore, as discussed above, the Toledo-Pereya and King references also fail to teach or suggest these Factor IXa compounds.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 25 on the ground of nonstatutory obviousness-type double patenting.

Summary

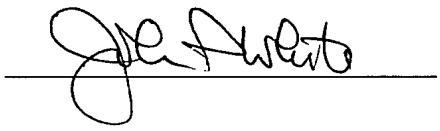
In view of amended claim 25 and the reasons set forth above, applicants maintain that the pending claims are in condition for allowance, and respectfully request that the Examiner issue a notice of allowance.

No fee, other than the enclosed $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invite the Examiner to telephone him at the number

provided below.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

5/17/07

John P. White — Date
Reg. No. 28,678